EXPERIMENTAL STUDIES ON HYPOTHERMIA

AUTHOR(S):

TOMIOKA, YOSHIRO

CITATION:

TOMIOKA, YOSHIRO. EXPERIMENTAL STUDIES ON HYPOTHERMIA. 日本外科宝函 1961, 30(1): 17-35

ISSUE DATE:

1961-01-01

URL:

http://hdl.handle.net/2433/207203

EXPERIMENTAL STUDIES ON HYPOTHERMIA

by

Yoshiro Tomioka

From the 2nd Surgical Division, Kyoto University Medical School
(Director : Prof. Dr. Yasumasa Aoyagi)

Received for publication Nov. 7, 1960

(PART I)

I. INTRODUCTION

Induced hypothermia is now increasingly attracting the attention of heart surgeons for its application on open heart surgery. Recently open heart surgery has been markedly developed by the use of artificial heart-lung apparatus. However, this method has many disadvantages as follows; Requirement of a large amount of heparinized blood, occurrence of cerebral or coronary air embolism, inability of maintenance of bloodless field for open heart surgery and the difficulty of management of this apparatus.

In comparison to this, induced hypothermia is very simple. Maintenance of bloodless field for open heart surgery, less incidence of cerebral or coronary air embolism and that a large amount of heparinized blood is not required are the excellent features of hypothermia.

The reduction of metabolism induced by hypothermia permits temporary circulatory occlusion. Under mild hypothermia it is possible to repair some congenital defects of heart, but the period of circulatory occlusion is too short for more complex intracardiac manipulation. In order to occlude total circulation for about 20 to 30 minutes adequate to perform the complex intracardiac operation, moderate or profound hypothermia has to be considered. However, the surgeons have encountered with the problem of ventricular fibrillation that seemed to occur more frequently at low body temperature than at normal. This ventricular fibrillation seems to be the fatal defect of hypothermia.

As is well known, hypothermic animals show an abnormal increase in hematocrit value and blood viscosity. Such a hemoconcentration and the increase of peripheral vascular resistence due to marked contraction of peripheral arteries burden the heart. Furthermore, increased capillary permeability and high venous pressure in hypothermia may result in edema of the heart muscle and excitatory and conduction system tissue of the heart. These factors described above should be the cause of ventricular fibrillation.

Nagase, in our laboratory, has reported that the essential fatty acid deficient animals had an increased capillary permeability and easily developed pulmonary edema following overhydration.

Our colleague, Kobayashi, Tamaki and Hanafusa have shown that the essen-

tial fatty acid deficient animals or patients had an increased capillary permeability and could not keep normal intra- and extra-cellular fluid balance after surgical operations.

These facts seem to indicate that administration of essential fatty acid protects against hemoconcentration caused by the abnormal increase of capillary permeability on cold stress. The present study was performed with this idea in mind.

Ⅱ. EXPERIMENTAL ANIMALS AND METHODS

A) Experimental Animals

1) Rats: Male albino rats of WISTAR strain supplied by the animal center in KYOTO University were used for the present study.

The weanling rats were divided into two groups. The first group was fed with synthetic diet practically free from fat, the second with synthetic fat diet. The weight composition of each diet is as follows. Fat diet: casein 20%, sesame oil 15%, starch 61%, mixed salts 4% and vitamine mixture 0.6g per 100g of food. Fat free diet: casein 20%, starch 76%, mixed salts 4% and vitamine mixture 0.6g per 100g of food.

2) Dogs: Healthy mongrel dogs weighing 6 to 12kg were used. They were divided into two groups; the first group was fed with natural diet, the second with the same diet and given 20% sesame oil emulsion or soya lecithin daily for about one week.

B) Methods

1) Rats were anesthetized with nembutal given intraperitoneally in a dose of 0.1cc per 100g, and cooled to a body temperature of 20°C in ice water. The body temperature was measured by an electrothermometer with its electrode inserted into abdominal cavity. At 36°, 28° and 20°C respectively, heparinized blood was collected via external juglar vein for the measurement of hematocrit value and blood viscosity. Hematocrit value was determined by centrifugation in WINTROBE'S tube at 3000 r.p.m. for 30 minutes. Blood viscosity was measured with HESS' viscosimeter.

2) Dogs were given atropin subcutaneously in a dose of 0.25 mg as premedication. Intubation was done under intravenous administration of pentothal sodium in a dose of 20 to 30 mg per kg. Anesthesia was maintained to control shivering under closed circuit anesthesia with ether and pure oxygen mixture. When shivering occurred during cooling, it was controlled by succinyl choline chloride given intravenously in a dose of 1 mg per kg or by increase of the concentration of ether in the closed circuit.

The body temperature was measured rectally by an electrothermometer.

Polyethylene tube was inserted into the femoral vein for the collection of blood sample and for the measurement of venous pressure after heparine was given intravenously in a dose of 1.5 to 2.0mg per kg.

Arterial pressure was measured by a mercury manometer directly connected to polyethylene tube inserted into the femoral artery.

Heart action was recorded electrocardiographically.

Dogs were cooled to 20°C by immersion method with supplement of head cooling with ice bags. The dogs were then removed from the ice bath and rewarmed in warm air to 33°C, ice bags on the head being kept until 30°C.

As to the experiment of circulatory occlusion, dogs were placed on the operating table and the left chest was entered through the 4th intercostal space. Circulatory occlusion was done by inflow occlusion following cross clamping the ascending aorta and pulmonary artery. Cardiac arrest was instituted with the use of cardioplegic agent into the aorta proximally to the clamp. The period of time to occlude circulation varied from 20 to 50 minutes. After release of occlusion cardiac massage was carried out until the cardiac action became normal. If fibrillation occurred, heart was immediately defibrillated by electric shock. Dogs were rewarmed by the intrathoracic rewarming method. This method was done by the continuous infusion into intrathoracic cavity of physiologic saline solution or RINGER's solution as warm as 30° to 45°C.

Throughout the process hyperventilation was performed and the animals were placed in the oxygen tent for about 12 hours after the removal of intratracheal tube at 33°C.

Ⅲ. RESULTS

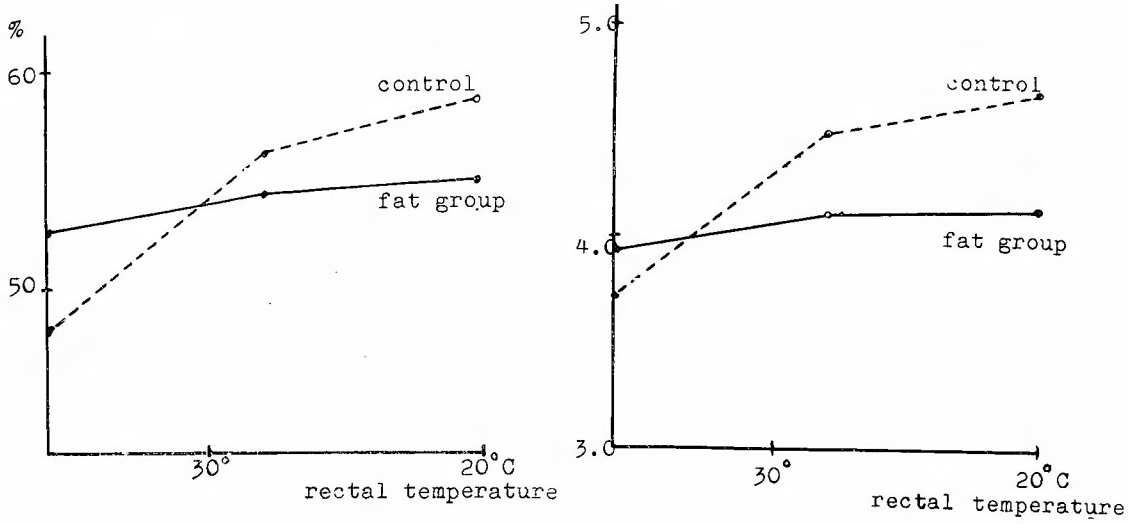
1) Observation on Induced Hypothermic Rats

Both groups of rats showed the increase in hematocrit value and blood viscosity, but the fat group showed less increase than the controls (Fig. 1).

2) Observation on Induced Hypothermic Dogs Whose Chests Were Not Entered

Fig. 1 A) Changes in hematocrit value of hypothermic rats during cooling. Hematocrit value (Mean value of each 5 rats)

B) Changes in blood viscosity of hypothermic rats during cooling. Blood viscosity (Mean value of each 5 rats)



a) Mortality: All of the fat group survived, but 2 of the controls died of ventricular fibrillation (Table 1).

Table 1

1) Fat group

Dog No.	Wt. of dog (kg)	Cooling time (min.)	Rewarming time (min.)	Temperature of dog (°C)	Result	Ventricular fibrillation
1	8.5	80	115	16.5	survived	no
4	9.3	120	155	18.0	survived	no
6	9.5	150	150	16.0	survived	no
8	7.0	100	200	18.0	survived	no
10	6.0	105	170	20.0	survived	no
11	12.0	160	170	16.0	survived	no
mean	8.7	119	160	17.4		

2) Control

Dog No.	Wt. of dog (kg)	Cooling time (min.)	Rewarming time (min.)	Temperature of dog (°C)	Result	Ventricular fibrillation
2	8.5	100	195	17.5	survived	no
3	13.0	210		16.0	died	yes
5	9.5	170	195	16.0	survived	no
7	7.5	160		16.0	died	yes
9	7.0	145	185	18.0	survived	no
12	8.5	190	225	18.0	survived	no
mean	9.0	163	200	17.0		

Vagostigmine was given in dogs No. 8, 9, 10 and 12.

b) Heart rate diminished linearly as the body was cooled. In initial stage during cooling shivering sometimes occurred accompanied with the temporary rise of heart rate, but when it was controlled heart rate returned to the expected levels (Fig. 2).

c) Mean time of the cooling period in the fat group was 119 minutes, and in the controls 163 minutes. Mean time of the rewarming period to 33° C in the fat group was 160 minutes, and in the controls 200 minutes. In short, the cooling and rewarming period in the fat group were shortened than in the controls (Table 1).

d) Femoral arterial pressure dropped gradually during cooling from 120/80 mm Hg at 37°C to 40/20 mmHg at 20°C. When shivering occurred during cooling blood pressure elevated temporarily, but it being controlled, this transient elevation returned to normal levels. As dogs were rewarmed, blood pressure was gradually restored to normal. However, in the fat group blood pressure was restored more readily to normal than in the controls (Fig. 2).

e) Under hypothermia there was a gradual elevation of venous pressure from 0 at 37 C to 100 to 200 mm of water at 20 C, but the fat group showed less elevation than the controls. During rewarming venous pressure was gradually reduced to 0 (Fig. 2).

Fig. 2 A) Changes in heart rate, arterial pressure, venous pressure and rectal temperature of hypothermic dogs in the controls.
Dog No. 4. Weight : 9.3 kg

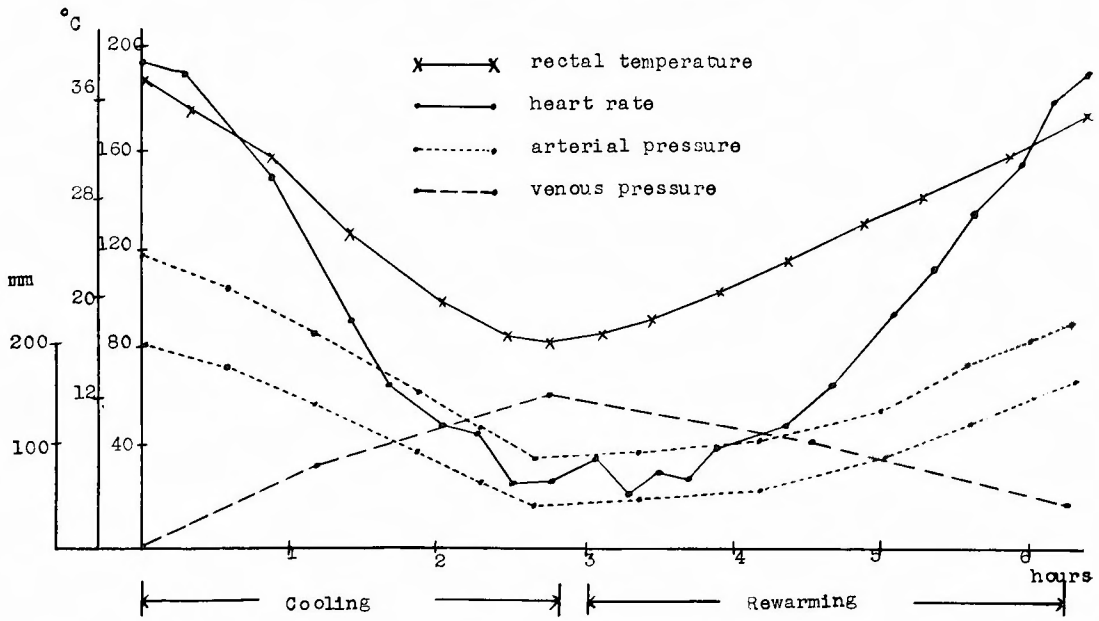
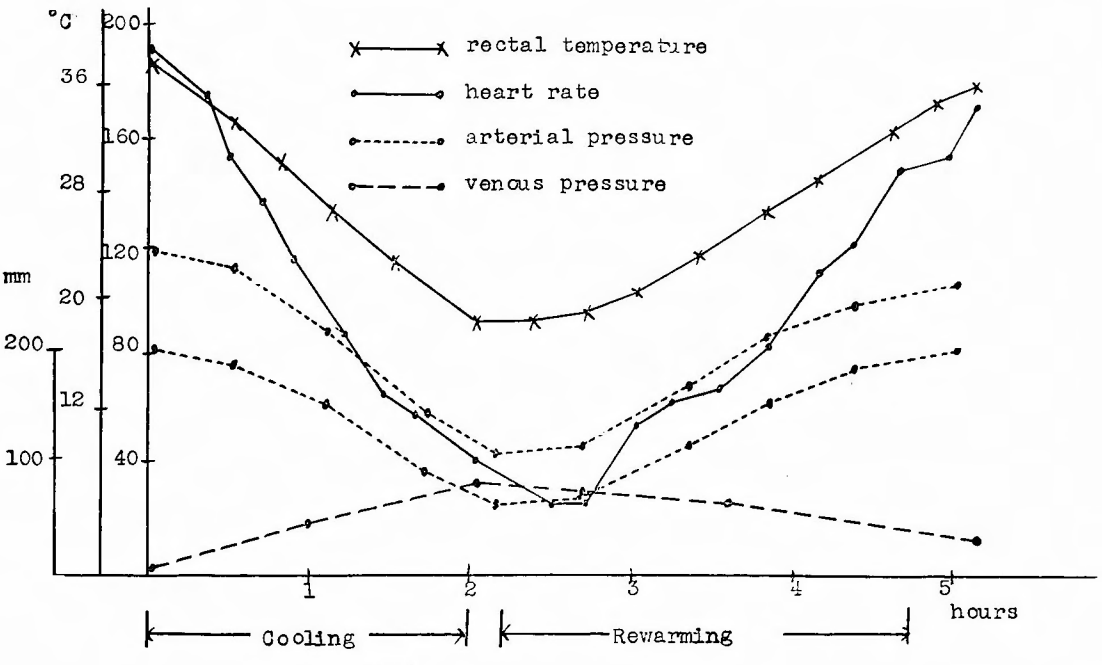
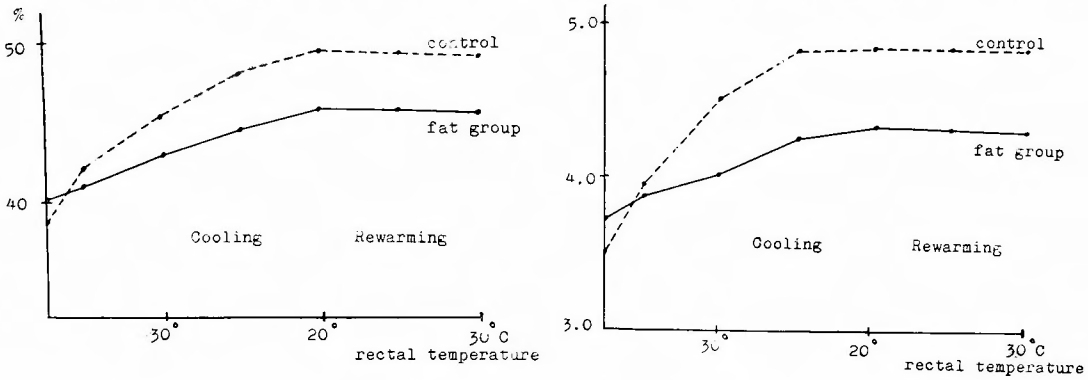


Fig. 2 B) Changes in heart rate, arterial pressure, venous pressure and rectal temperature of hypothermic dogs in the fat group.
Dog No. 5. Weight : 9.5 kg



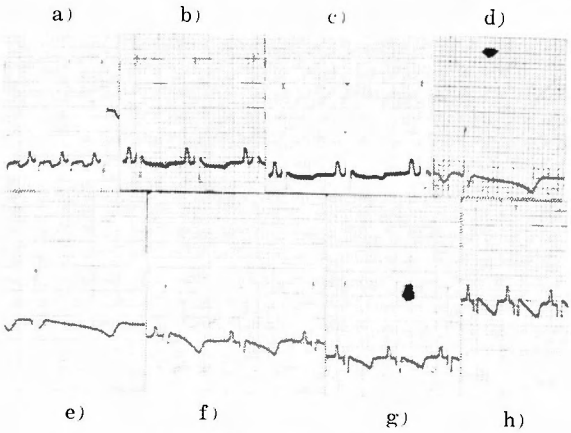
f) In general, as dogs were cooled hematocrit value and blood viscosity increased abnormally, but in the fat group these showed less increase than in the controls. During rewarming maintenance of the highest levels in hematocrit value and blood viscosity was observed in both groups (Fig. 3).

Fig. 3 A) Changes in hematocrit value of hypothermic dogs during cooling and rewarming.
Hematocrit value (Mean value of each 4 dogs)
B) Changes in blood viscosity of hypothermic dogs during cooling and rewarming.
Blood viscosity (Mean value of each 4 dogs)



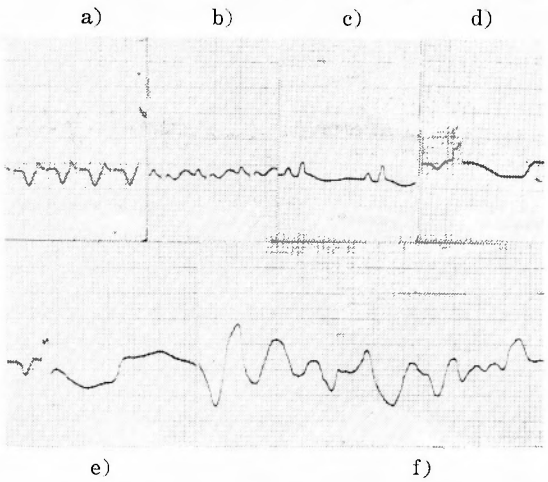
g) As the body was cooled, the prolongation of R-R, P-R and S-T, the negative P and notching or slurring of R were observed electrocardiographically, but as rewarming was progressed these were restored to normal. 2 of the controls incurred ventricular fibrillation at the initial stage of rewarming (Fig. 4).

Fig. 4. A) Electrocardiographic tracings
(Lead II)



a) at 37°C during cooling
b) at 30°C during cooling
c) at 25°C during cooling
d) at 20°C during cooling
e) at 20°C during rewarming
f) at 25°C during rewarming
g) at 30°C during rewarming
h) at 33°C during rewarming

B) Electrocardiographic tracings (Lead Ⅱ)



a) at 37°C during cooling
b) at 30°C during cooling
c) at 25°C during cooling
d) at 18°C during cooling
e) at 18 C during rewarming
f) Ventricular fibrillation

h) As prevention of ventricular fibrillation, vagostigmine was given subcutaneously into 4 dogs in a dose of 0.05 ml per kg at 25°C during cooling. Ventricular fibrillation was not observed in this group under hypothermia.

3) Observation on Induced Hypothermic Dogs Whose Chests Were Entered

Dogs were subjected to total circulatory occlusion for a period varied from 20 to 50 minutes and right ventriculotomy was performed.

In the controls 8 out of 9 dogs incurred ventricular fibrillation, but in the fat group only 4 out of 27 dogs.

In the fat group 22 out of 27 dogs survived, but in the controls only 4 out of 9 dogs.

2 dogs of the fat group whose anterior descending branches of coronary arteries were ligated 1 month prior to the experiment were successfully subjected to circulatory occlusion for a period varied from 24 to 26 minutes with help of hypothermia below 20°C.

5 dogs were subjected to circulatory occlusion for 50 minutes under hypothermia from 18° to 22°C. All 5 dogs survived.

Ⅳ. DISCUSSION

Nagase, in our laboratory, has demonstrated that the essential fatty acid deficient animals had an increased capillary permeability and easily developed water intoxication and pulmonary edema following overhydration.

Our colleague, Kobayashi observed that administration of 20% sesame oil emulsion in dogs before and after gastrectomy maintained the blood colloidal osmo-

Table 2

1) Control

Dog No.	Wt. of dog (kg)	Temperature of dog (℃)	Occlusion time(min.)	Ventricular fibrillation	Result
14	6.7	20.0	20	yes	died
18	12.0	18.0	18	yes	survived
20	8.0	17.0	20	no	died (Filaria emboli)
21	12.7	18.0	25	yes	survived
23	11.6	19.0	25	yes	survived
25	6.8	18.0	22	yes	survived
27	6.8	19.0	20	yes	died (Pulmonary edema)
41	7.7	15.0	32	yes	died (Fibrillation)
42	10.0	19.0	21	yes	died (Fibrillation)

2) Fat group

Dog No.	wt. of dog (kg)	Temperature of dog (℃)	Occlusion time (min.)	Ventricular fibrillation	Result
13	6.2	18.5	20	no	survived
15	6.2	18.5	40	yes	survived
16	6.7	20.0	31	no	survived
17	6.6	19.0	30	no	survived
19	8.5	18.0	20	no	survived
22	9.5	18.0	21	no	survived
24	7.0	18.5	31	no	survived
26	9.2	19.0	20	yes	survived
28	5.8	19.5	30	no	survived
29	11.0	18.0	20	no	survived
30	6.3	17.0	21	no	survived
31	6.7	19.0	24	no	survived
32	10.0	19.5	26	no	survived
33	8.2	19.0	30	no	survived
34	9.5	19.5	21	no	died (Pulmonary edema)
35	8.5	18.0	30	no	died (Pulmonary edema)
36	6.7	18.0	30	no	died (Pulmonary edema)
37	5.8	19.0	21	no	died (Pulmonary edema)
38	5.7	19.0	22	no	died (Pulmonary edema)
39	6.1	18.5	20	yes	survived
40	5.8	19.5	20	no	survived
43	8.5	18.3	50	no	survived
44	7.5	18.0	50	no	survived
45	7.5	19.5	50	yes	survived
46	6.8	21.0	50	no	survived
47	8.0	22.0	50	no	survived
48	7.6	19.0	20	no	survived

All dogs of both groups were given vagostigmine subcutaneously in a dose of 0.25mg.
Anterior descending branches of coronary arteries of dogs No. 31 and 32 were ligated 1 month prior to the experiment.

tic pressure and volume of the intra- and extra-cellular fluid at about the normal level in the postoperative state.

TAMAKI, in our laboratory, showed the same data in clinical cases of gastrectomy patients. These effects of fat administration may be attributed to the action of essential fatty acid. Essential fatty acid seems to play the main role in preventing the increase of capillary permeability.

D'AMATO and HEGNAUER have showed that the hematocrit value and blood viscosity abnormally increased in the hypothermic dogs. In short, when animals were cooled, blood is concentrated. It is obviously true that abnormal low body temperature induces paralytic dilatation and increased permeability of capillaries.

Many observers have demonstrated that peripheral circulatory resistence abnormally increased because of marked contraction of peripheral arteries in hypothermia.

As the body temperature falls, cardiac output progressively declines and blood pressure drops in spite of increased peripheral circulatory resistence. Blood is accumulated in the venous side of the systemic circulation and this volume changes are reflected in increasing venous pressure because of the absence of the flexibility of the venous reservoirs due to the marked contraction of peripheral veins.

In order to avoid hemoconcentration under hypothermia, FUJIWARA developed the following procedure : Blood was diluted by the replacement of a moderate amount of blood with the same amount of physiologic saline solution during cooling and the procedure was reversed during rewarming. Such procedures protected hypothermic dogs against ventricular fibrillation and shortened the cooling and rewarming period.

The present study was started under the hypothesis that essential fatty acid prevents the hemoconcentration in hypothermia and reached to the expected results. With administration of 20% sesame oil emulsion, hypothermic animals showed less increase in hematocrit value and blood viscosity than the controls and did not incur fibrillation. Moreover, cooling and rewarming period was markedly shortened.

Our colaborator, SAITO observed that the electrical threshold value for ventricular fibrillation at 20°C was higher in the essential fatty acid sufficient group than the controls. In the former it showed a mean value of 13 volts and in the latter 4 volts.

High venous pressure results in disturbance of the coronary venous return. Increased capillary permeability and high venous pressure might bring about edema of the heart muscle and excitatory and conduction system tissue of the heart.

YOSHII et al. have stated that under hypothermia continuous intravenous infusion of hypertonic saline solution was much effective for the prevention of ventricular fibrillation and the dogs given hypertonic saline solution showed a higher electrical threshold value for ventricular fibrillation than the controls.

This effect seems to be ascribed not only to ion concentration, but also to the hypertonicity of infused solution. Therefore, edema of the heart muscle may be reduced with the administration of hypertonic saline solution.

According to YOSHII et al. water content of the heart muscle given continuously hypertonic saline solution during cooling was 76%, and that of the controls

78%. This indicates that edema of the heart muscle is a little greater in the controls than in the group given hypertonic saline solution.

Considering these facts, there seems to be some apparent relationship between the incidence of ventricular fibrillation and the edema of the heart muscle. The load on the heart due to increased peripheral resistence and venous pressure and the edema of the heart muscle seem to be the main causes of the ventricular fibrillation under hypothermia.

Many observers have demonstrated that hypoxia might be the cause of ventricular fibrillation. In the present study, hypoxia was avoided by the following procedures: 1) Cardiac output was increased by accelaration of heart rate with the use of pacemaker stimulator at the sinus node before circulatory occlusion, 2) after release of occlusion coronary and cerebral blood flow was increased temporarily clamping the descending aorta and 3) hyperventilation was performed throughout the experiment.

Montgomery et al. have reported that prostigmine had a marked antifibrillatory effect under induced hypothermia, particularly when it was administered via coronary perfusion immediately before circulatory occlusion, its effect was dramatic. They also stated that the low systemic arterial pressure activated the carotid sinus by hypothermia, resulting in a lack of vagal impulses to the heart, an increase in sympathetic impulses to the heart and an intense vasoconstriction mediated by sympathetic fibers, and in respect of the antifibrillatory effect this drug became of note.

Garcia Ramos et al. showed that acetylcholine depresses the oxygen consumption of frog's and turtle's heart. From this observation, use of prostigmine seems to be rational for prevention of ventricular fibrillation.

In the present study, dogs were given subcutaneously in a dose of 0.25 mg of vagostigmine at 25°C during cooling. This group rarely incurred ventricular fibrillation except dogs in the controls whose chests were entered.

Under hypothermia, the incidence of ventricular fibrillation is higher than at normal body temperature, and when it occurred, normal ventricular rhythm cannot so readily be restored. During fibrillation heart massage is necessary procedure and this brings about the mechanical impairment of the heart muscle. And it is natural that the longer the massage, the more severe the impairment. Electric shock for defibrillation, too, insults heart muscle by burning and its late mortality becomes higher.

With the use of cardioplegic agent, surgeons can obtain the motionless operative field for intracardiac manipulation and moreover, cerebral or coronary air embolism does not occur.

Without the use of cardioplegic agent upon circulatory occlusion fibrillation occurs, particularly after manipulation of heart and upon release of occlusion.

Oxygen consumption of fibrillating heart is higher than normal and theoretically metabolism of normal heart might be higher than that of the arrested one.

In the present study, Young's solution (0.54 g potassium citrate and 2.47 g

magnesium sulfate per 100 ml : pH 7.4 with sodium bicarbonate) was used as a cardioplegic agent and normal heart rhythm was obtained within about 2 minutes after release of occlusion by cardiac massage.

MONTGOMERY et al. have stated that fibrillating heart lost potassium and coronary venous blood gained it.

HOOKER found that the fibrillating isolated heart lost potassium to the perfusion medium and the fibrillation could be converted by the addition of potassium medium. From this observation he suggested that the potassium added to the perfusion fluid caused the fibrillating myocardium to make it up its potassium deficiency and by so doing restored normal ventricular rhythm.

SWAN et al. found that the fibrillating hypothermic heart could rarely be converted to a normal rhythm by massage and electric shock. However, when coronary arteries of the fibrillating heart were perfused with KCl solution (1 mEquiv./ml), the fibrillation could usually be converted spontaneously or with the use of electric shock.

In the present study, when defibrillatory procedures were not effective, repetition of defibrillatory procedures after cardiac arrest using YOUNG's solution was often effective.

SWAN et al. have reported that electric shock after coronary perfusion of prostigmine was effective for defibrillation.

This seems to be the action of the accumulation of acetylcholine in cell membrane, which makes the rate of movement of potassium across the myocardium membrane increased and the restoration of the intracellular potassium more efficient.

When fibrillation continued for a long time, heart loses potassium and becomes hypoxic and defibrillation becomes more difficult. In this case, firstly, the restoration of intracellular potassium deficiency and sufficient oxygen supply must be performed and then defibrillatory procedures be carried out.

V. CONCLUSION

1) With the use of 20% sesame oil emulsion or soya lecithin for about one week before the induction of hypothermia, the abnormal rise in hematocrit value and blood viscosity was prevented and the incidence of ventricular fibrillation was rare.

2) The fat group of dogs showed a shorter period of time to cool and rewarm than the controls.

3) YOUNG's solution is an excellent cardioplegic solution.

4) Hyperventilation, cross clamping the descending aorta before circulatory occlusion and after release of occlusion and the use of pacemaker stimulator before circulatory occlusion, these seem to be effective for prevention of ventricular fibrillation.

5) Vagostigmine is an excellent antifibrillatory drug.

(PART II)

I. INTRODUCTION

Recently open heart surgery has been performed successfully under induced hypothermia in which the reduction of metabolism enables temporary occlusion of circulation for an adequate period of time to perform intracardiac manipulation without observable damage to vital organs.

Many observers have shown that the metabolic rate of dogs under induced hypothermia fell linearly with the lowering of the body temperature and the rate at 20°C (rectal temperature) was only about 20% of control.

It has been reported that in normothermia the safe period of time to occlude circulation was only about 3 minutes.

Young et al. have stated that hypothermia to 25°C apparently prolonged this safe time to 5 or 6 minutes.

Blair et al. have reported that circulatory occlusion of 8 minutes at a body temperature not lower than 28°C was done and relatively safe.

Mavor et al. have stated that at the temperature range of 25° to 30°C, 20 minutes was regarded as the critical limit for circulatory arrest.

Lam et al. have reported that when the rectal temperature was lowered to 22 °C, it was possible to arrest the heart for 30 minutes with complete recovery.

As is described above, many observers have different opinions as to the safe time limit of circulatory occlusion in relation to the various temperature.

The present study was done to determine the rate of metabolism by measuring polarographically the oxygen consumption of the brain of dogs in vivo in normothermia and in hypothermia.

II. EXPERIMENTAL ANIMALS AND METHODS

Adult healthy mongrel dogs weighing 8 to 12kg were used. Atropin was given subcutaneously in a dose of 0.25 mg as premedication. Intubation was done using pentothal sodium intravenously in a dose of 30 mg per kg. Anesthesia was maintained to control shivering by closed circuit anesthesia with ether and pure oxygen mixture.

Dogs were cooled by immersion method and the body temperature was measured rectally by an electrothermometer.

Parietal lobe of the brain was exposed and prepared for measuring oxygen tension polarographically. The polarographic electrode was placed on the surface of parietal lobe relatively free from blood vessels.

EEG was obtained by fronto-occipital lead.

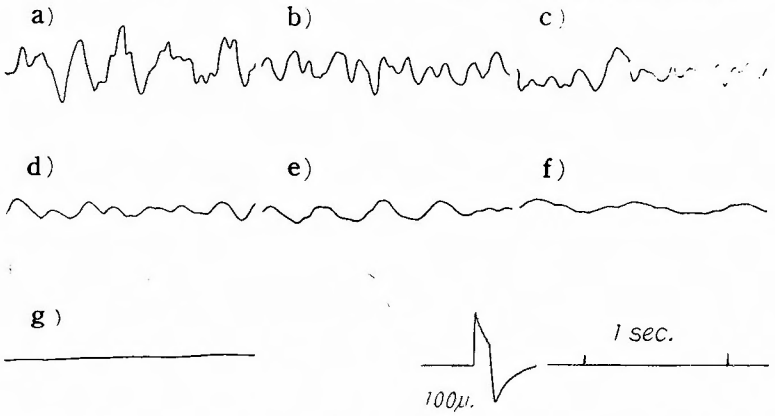
Thoracotomy was performed through the left 4th intercostal space and circulatory occlusion was done by cross clamping the ascending aorta and pulmonary artery.

The current flow resulting from the reduction of oxygen was continuously recorded by polarography and EEG was also observed. Polarographic current flow which reflects brain oxygen tension was expressed as a percentage change from control levels.

Ⅲ. RESULTS

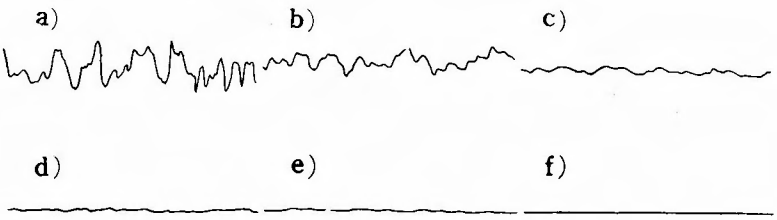
1) EEG: As the body was cooled, the amplitude and frequency in EEG became lower and lower and disappeared below 15°C (Fig. 5).

Fig. 5. A) Electroencephalographic tracings during cooling (Fronto-occipital lead)



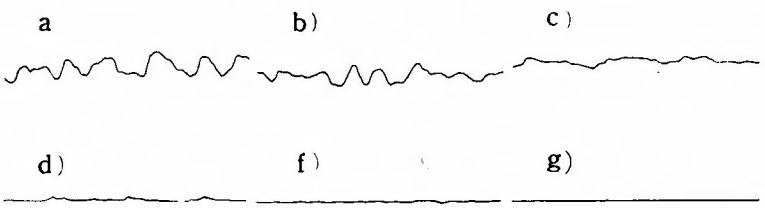
a) at 38°C b) at 33°C c) at 28°C d) at 24°C e) at 20°C f) at 16°C g) at 15°C

B) Electroencephalographic tracings after circulatory occlusion at 37°C (Fronto-occipital lead)



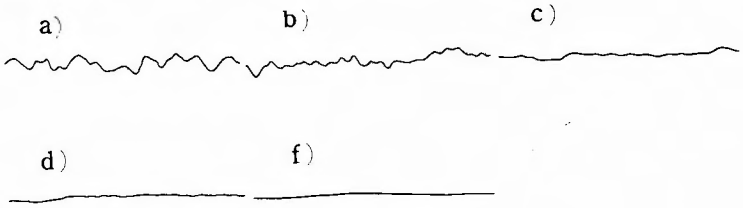
a) before circulatory occlusion
b) 10 seconds after circulatory occlusion
c) 20 seconds after
d) 30 seconds after
e) 40 seconds after
f) 50 seconds after

C) Electroencephalographic tracings after circulatory occlusion at 28°C (Fronto-occipital lead)



a) before circulatory occlusion
b) 10 seconds after circulatory occlusion
c) 20 seconds after
d) 30 seconds after
f) 40 seconds after
g) 50 seconds after

D) Electroencephalographic tracings after circulatory occlusion at 25°C (Fronto-occipital lead)



a) before circulatory occlusion
b) 30 seconds after circulatory occlusion
c) 1 minute after
d) 1 minute and 30 seconds after
f) 2 minutes after

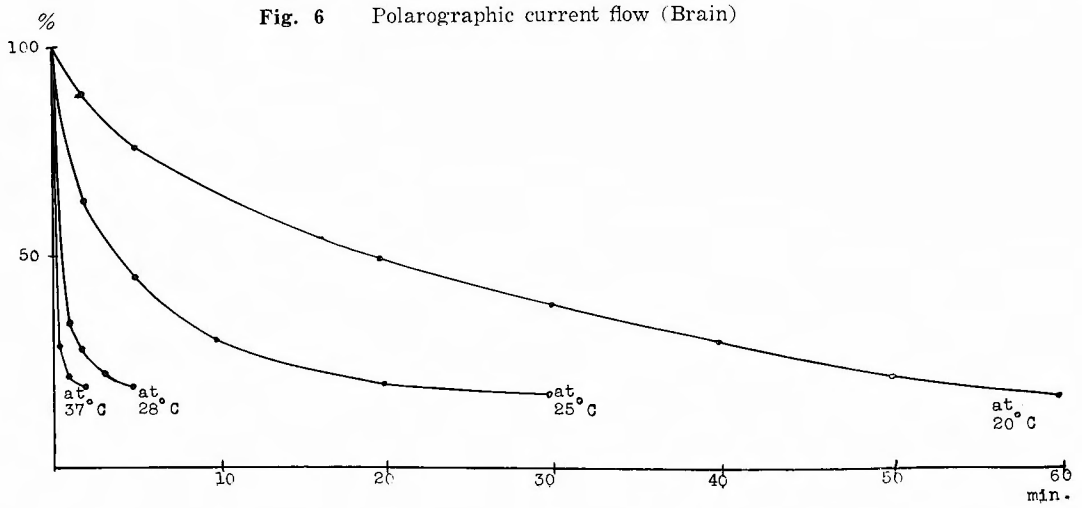
After circulatory occlusion in normothermia, the amplitude and frequency in EEG became low rapidly and disappeared within about 50 seconds. At 28°C EEG disappeared about 50 seconds after circulatory occlusion and at 25°C about 2 minutes after circulatory occlusion.

2) Polarographic Current Flow : Immediately after circulatory occlusion in normothermia current flow fell rapidly and precipitously and within about 1 minute it reached to a level of 20% of the control reading and then stabilized at the same level as soon as the fall of oxygen tension was completed.

After circulatory occlusion at 28°C, the current flow fell rapidly and stabilized on a level of 20% of the control reading within 6 minutes.

Following circulatory occlusion at 25° or 20°C, current flow showed slow falling, and at 25°C stabilization of the reading was attained within about 30 minutes and at 20°C within 60 minutes (Fig. 6).

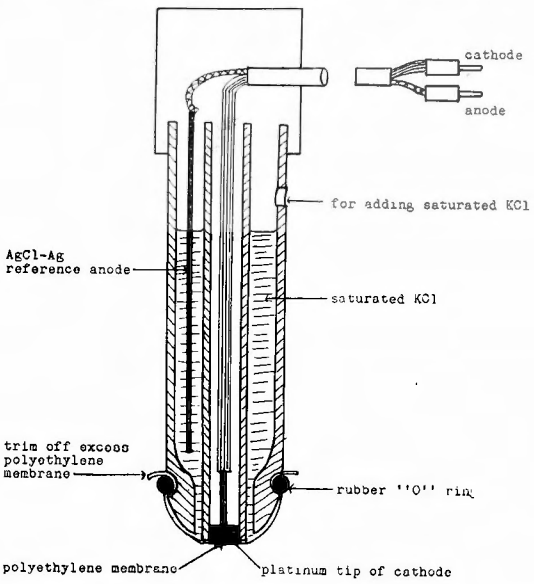
Fig. 6 Polarographic current flow (Brain)



Ⅳ. DISCUSSION

Polarographic electrode used in the present study was the CLARK polarograph electrode. Polarographic cathod and anode were included in a tube filled with saturated KCl solution and the electrodes' tip was covered with very thin polyethylene membrane (Fig. 7).

Fig. 7 CLARK POLAROGRAPH ELECTRODE



Polarographic apparatus used in the present study was produced in YANAGIMOTO Co. Ltd. in Japan. In this apparatus the voltage at which the diffusion limiting current of oxygen flowed was between -0.4 and -0.7 volts, and in the present study the cathode was maintained at -0.6 volts in respect to a non-polarizable anode. In such a circumstance, current flow was proportional to the oxygen content of the tissue. This cathode is to measure oxygen brought to it by free diffusion of the gas through polyethylene membrane.

Many observers have shown that if the saline solution was agitated current flow from a cathode in saline solution of the same tension of oxygen might be increased five times or more.

Absence of this stirring effect caused by abrupt cease of blood flow seems to influence the data, because the brain surface contains blood vessels more or less.

Abrupt and precipitous fall of current flow after circulatory occlusion in normothermia is interpreted as to be caused not only by the cerebral hypoxia due to the oxygen consumption of cerebral cells, but also by the absence of stirring effect by the abrupt cessation of blood flow.

In respect of the abrupt fall of current flow after circulatory occlusion at 28° C the same is true, but the influence of absence of stirring effect seems to be less than in normothermia because of the relative decrease of blood flow at that tem-

perature.

Blood flow being much decreased and blood vessels markedly contracting at 25° or 20°C, the influence of absence of stirring effect after circulatory occlusion seems to be rarely apparent and current flow falls very slowly.

Considering this stirring effect, the stabilization time of current flow after circulatory occlusion at 37° or 28°C seems to be a little bit prolonged.

It is suggested that, when current flow stabilizes, cerebral cells are exhausted and cannot consume oxygen, but before it stabilizes they are yet consuming oxygen and can restore to normal by additional sufficient oxygen supply.

On this hypothesis, dogs were subjected to circulatory occlusion for 50 minutes at 18° to 22°C and all successfully resuscitated (Table 2).

Considering these facts, circulatory occlusion seems to be limited at about the level of 20% of the control reading.

With the help of hypothermia below 20°C it seems to be safe to occlude circulation even for about 50 to 60 minutes. Because, though at this temperature ventricular fibrillation occurs frequently, the blood pressure produced by cardiac massage may be sufficient to supply the blood to vital organs in which metabolic rate is markedly reduced.

At 25°C the safe period of time for circulatory occlusion seems to be theoretically about 30 minutes. However, at this temperature it takes about 5 minutes to regain sufficient blood pressure after release of occlusion. Therefore, the safe time limit to occlude circulation at 25°C seems to be about 25 minutes practically.

At 28°C, even if ventricular fibrillation occurs after release of occlusion defibrillation can be readily accomplished to restore the blood pressure. Considering this fact, the safe period to occlude circulation at 28°C seems to be about 6 minutes.

V. SUMMARY AND CONCLUSION

1) The changes of nervous system was observed polarographically and electroencephalographically after circulatory occlusion.

2) After circulatory occlusion cerebral oxygen tension decreased and stabilized on an average level of about 20% of the control reading.

a) In normothermia current flow reduced rapidly and precipitously and stabilized about 1 minute after circulatory occlusion.

b) At 28°C current flow fell rapidly and stabilized about 6 minutes after circulatory occlusion.

c) At 25°C current flow reduced slowly and stabilization occurred at about 30 minutes after circulatory occlusion.

d) At 20°C current flow reduced very slowly and it took about 60 minutes to stabilize after circulatory occlusion.

3) As the body temperature fell, the amplitude and frequency in EEG disappeared below 15°C.

After circulatory occlusion EEG disappeared in about 50 seconds at 37° and 28°C, about 2 minutes at 25°C.

4) Circulatory occlusion of 50 minutes at 18° to 22°C was safe in hypothermic dogs.

5) Considering the results, the safe period of time to occlude circulation seems to be about 50 to 60 minutes below 20°C, 25 minutes at 25°C and 6 minutes at 28°C.

The author wishes to express his sincere gratitude to Dr. Y. Hikasa, the lecturer of our clinic, for his helpful suggestion and kind guidance in the course of the work.

The author wishes to thank his collaborators Dr. H. Shirotani, Dr. T. Kuyama, Dr. A. Saito and Dr. K. Kuwana for their kind advice and help.

REFERENCES

1) Bigelow, W. G., Mastard, W. T. and Evans, J. G. : Some Physiologic Concepts of Hypothermia and Their Application to Cardiac Surgery. J. Thoracic Surg., **28**, 463, 1954.
2) Blades. B. and Pierpont, H. C. : A Simple Method for Inducing Hypothermia. Ann. Surg., **140**, 557, 1954.
3) Blair, E., Austin, R. R., Blount, S. G. and Swan, H. : A Study of the Cardiovascular Changes during Cooling and Rewarming in Human Subjects Undergoing Total Circulatory Occlusion. J. Thoracic Surg., **33**, 707, 1957.
4) Burr, G. O. : Significance of the Essential Fatty Acid. Fed. Proc., **1**, 224, 1942.
5) Clark, L. C., Wolf, R., Granger, D. and Taylor, Z. : Continuous Recording of Blood Oxygen Tension by Polarography. J. Appl. Physiol., **6**, 189, 1953.
6) Connely, C. M. : Methods for Measuring Tissue Oxygen Tension. Fed. Proc., **16**, 861, 1957.
7) DA Costa, I. A., Ratcliffe, J. W. and Gerbode, F. : Studies on the Physiological Effects of Hypothermia in Chronic Experimental Cyanosis. Ann. Surg., **140**, 821, 1957.
8) D'Amato, H. E. and Hegnauer, A. H. : Blood Volume in the Hypothermic Dog. Am. J. Physiol., **173**, 100, 1953.
9) Deterlng, R. A., Nelson, E., Bohnslay, S. and Howland, W. : Study of Basic Physiologic Changes Associated with Hypothermia. Arch. Surg., **70**, 87, 1955.
10) Edwards, W. S., Tuluy, S., Reber, W. E., Siegel, A. and Bing, R. J. : Coronary Blood Flow and Myocardial Metabolism in Hypothermia. Ann. Surg., **139**, 279, 1954.
11) Feder, E. J., Fisher, B. and Lee, S. H. Rewarming Following Hypothermia of Two to Twelve Hours : I. Cardiovascular Effects. Ann. Surg., **147**, 515, 1953.
12) Fujiwara, K. : Studies on the General Hypothermia and the Induction of the Ventricular Fibrillation. J. J. S. S., **57**, 1129, 1956.
13) Garcia Ramos, J. and Tlalpan, D. F. : Ventricular Fibrillation in Artificial Hypothermia. J. Thoracic Surg., **31**. 635, 1956.
14) Hanafusa, S. : Clinical Studies on the Nutritional Effects of Fat Emulsion Administered Intravenously and by Usual Tube Feeding. Arch. jap. Chirur., **28**, 1356, 1959.
15) Hegnauer, A. H., Shriber, W. J. and Haterius, H. O. : Cardiovascular Response of the Dog to Immersion Hypothermia. Am. J. Physiol., **161**, 455, 1950.
16) Hikasa, Y. et al. : Parenteral Administration of Fats. I. Fat Metabolism in Vivo, Studied with Fat Emulsion. Arch. jap. Chirur., **27**, 396, 1958.
17) Hikasa, Y. et al. : Parenteral Administration of Fats. II. Clinical Application of Fat Emulsion. Ibid., **27**, 736, 1958.
18) Hikasa, Y. et al. : Significance of Fat Nutrition. I. Surgical Diagnosis and Treatment, **1**, 332, 1959.
19) Hikasa, Y. et al. : Significance of Fat Nutrition. II. Ibid., **2**, 117, 1960.
20) Hikasa, Y. et al. : Significance of Fat Nutrition. III. Ibid., **2**, 253, 1960.
21) Hikasa, Y. et al. : Significance of Fat Nutrition. IV. Ibid., **2**, 386, 1960.
22) Hikasa, Y. et al. : Significance of Fat Nutrition. V. Ibid., **2**, 648, 1960.
23) Hikasa, Y. et al. Significance of Fat Nutrition. VI. Ibid., **2**, 931, 1960.
24) Kaplan, S., Matthews, E. C., Schwab, L. and Clark, L. C. : Oxygen Availability to the Brain

during Inflow Occlusion of the Heart in Normothermia and Hypothermia. J. Thoracic Surg., **32**, 576, 1956.
25) Kehar, N. D. and Hooker, D. R. : Evidences of an Altered Tissue State in Ventricular Fibrillation. Am. J. Physiol., **112**, 301, 1935.
26) Kirby, C. K., Jensen, C. M. and Johnson, J. : Defibrillation of the Ventricles under Hypothermic Conditions. Arch. Surg., **68**, 663, 1954.
27) Kobayashi, M. . unpublished.
28) Kramàr, J. and Levine, V. E. : Influence of Fats and Fatty Acids on the Capillaries. J. Nutrition, **50**, 149, 1953.
29) Lam, C. R., Geoghegan, T. and Lepore, A. : Induced Cardiac Arrest for Intracardiac Surgical Procedures. J. Thoracic Surg., **30**, 620, 1955.
30) Mavor, G. E., Harder, R. A., Emerson, G. L. and Mahoney, E. B. : Procaine Amide in Hypothermia. J. Thoracic Surg., **31**, 744, 1956.
31) Montgomery, A. V., Prevedel, A. E. and Swan, H. : Prostigmine Inhibition of Ventricular Fibrillation in the Hypothermic Dog. Circulation, **10**, 721, 1954.
32) Nagase, M. : Experimental Study on Pathogenesis of Acute Postoperative Pulmonary Edema. Arch. jap. Chirur., **29**, 67, 1960.
33) Riberi, A., Siderys, H. and Shumacker, H. B. : Ventricular Fibrillation in the Hypothermic State : 1. Prevention by Sino-auricula Node Blockade. Ann. Surg., **143**, 216, 1956.
34) Rodbard, S., Saiki, H., Malin, A. and Young, C. : Significance of Change in Plasma and Extracellular Volume in Induced Hypothermia and Hyperthermia. Am. J. Physiol., **167**, 485, 1951.
35) Saito, A. : unpublished.
36) Shumacker, H. B., Jr., Riberi, A., Boone, R. D. and Kajikuri, H. : Ventricular Fibrillation in the Hypothermic State. : Ⅳ. The Role of Extrinsic Cardiac Innervation. Ann. Surg., **143**, 223, 1956.
37) Shumway, N. E. and Lewis, F. J. . Induced Ventricular Fibrillation for Experimental Intracardiac Surgery under Hypothermia. Ann. Surg., **143**, 230, 1956.
38) Tamaki, M. · unpublished.
39) Virtue, R. W. . Hypothermic Anesthesia. Charles C. Thomas, Springfield, Illinois, 1955.
40) Yoshii, N. : Physiological Problems of Hypothermia, Especially the Antifibrillatory Effect of Hypertonic Saline Solution. Studies on Cardiac Surgery. Igakushoin, 351, 1958.
41) Young, W. G., Sealy, W. C., Brown, I. W., Hewit, W. C., Callaway, H. A., Merrit, D. H. and Harris, J. S. : A Method for Controlled Cardiac Arrest as an Adjunct to Open Heart Surgery. J. Thoracic Surg., **32**, 604, 1956.

和 文 抄 録

低体温麻酔法の基礎的研究

京都大学医学部外科学教室第2講座 （指導：青柳安誠教授）

富 岡 啓 郎

心臓外科への低体温麻酔法の応用が近時とみに注目されるようになつて来たが，これは体温の下降に伴い，個体の新陳代謝も亦低下するので，この特性を利用すれば，心内手術操作を確実に行うに必要にして充分な時間だけ血流を遮断し得るからである．と同時にまた，人工心肺応用時に較べて，その操作が簡単で経費（ヘパリン血）の節約ができるばかりでなく，心内手術操作を行うにあたつても完全な Dry field が得られ，手術操作に極めて便利であり，また人工心肺応用時のように，脳及び冠状動脈の空気栓塞を招く怖れも殆んどないなど数々の利点をも有しているからである。

本実験に於ては，各種体温に於ける全血流遮断時の大脳皮質表面の酸素張力をポーラログラフィー法を駆使，応用することによつて連続的に測定すると共に，試獣を各種の低体温麻酔下に開胸し，全血流遮断下に右心室切開を行い，次いでこれを縫合閉鎖し，閉胸するという実際に即した実験をも同時に併せ行い，斯る際の当該試獣の長期生存率をも求め，この両者の実験成績から，各種体温時の全血流遮断の許容時間を決定した．

その結果，体温20℃以下に於ては50分以上の，体温20℃～22℃に於てすらも50分程度の全血流遮断の可能なことを知つたが，また体温25℃では25分程度，体温28℃に至れば6分内外がその安全限界であることをも略々明らかならしめることが出来たのである．

併し，従来はたといこのような全血流遮断許容時間が得られても，体温28℃以下になれば，屢々心室細動が発生し，それを安全に施行することは困難であるとされて来たので，われわれは更に，心室細動の発生防止対策についても討究したのである．ふつう低体温麻酔時に際しては，必然的に毛細血管透過性が異常に亢進し，心筋組織は浮腫状を呈し，同時に循環血液は著しく濃縮して，そのために末梢抵抗も増大し，遂にはそれが心臓に対し著しい負担を及ぼす結果ともなつて，心室細動発生の一大要因となり得ることが指摘されているので，本研究に於ては専ら如何にすればかゝる低体温麻酔時の毛細血管透過性の異常な亢進を防止することが出来るか，またそれによつて果して心室細動の発生をも抑制し得るかという点を討究した．その結果，麻酔前に予め充分量の不可欠脂酸を経口的あるいは経静脈的に投与しておくことが最善の予防対策であることを明らかにし，而もそれによつて心室細動の発生をもよく防止し得ることを立証し得た．そしてかかる予防対策を構ずることによつて，低体温麻酔法の安全性は非常に昂められ，実験的開心術を施行した試獣に於ても極めて良好な長期生存率が得られるようになつた．